In the Claims:

Please cancel Claims 10-15 without prejudice or disclaimer.

Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action mailed July 18, 2002 (the Action). Claims 1-15 are pending in the present application. Claims 10-15 have been cancelled without prejudice or disclaimer to the filing of a divisional application. Thus, Claims 1-9 are under examination. Applicants have amended the Abstract of the Disclosure pursuant to suggestions presented by the Examiner. Such amendments relate to form only, and do not pertain to issues relative to the prior art, and are fully supported by the application as originally filed.

Claims 1-15 are subject to a Restriction Requirement. Claims 1-9 stand rejected under 35 U.S.C. § 103 as being obvious over the cited references. The concerns raised by the Examiner are addressed below as set forth in the Action.

I. Specification

Applicants have amended the specification pursuant to the Examiner's suggestions. The Abstract of the Disclosure as amended is in narrative form composed of clear and concise language.

Accordingly, Applicants respectfully request that the objection to the Abstract of the Disclosure be withdrawn.

II. Restriction Requirement

In furtherance of the provisional election to prosecute the claims of Group I made during a telephone conversation with the Examiner on June 26, 2002, Applicants hereby affirm the election of Group I (Claims 1-9, drawn to a method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria, comprising administering to said bacteria a test compound in an effective antivirulence amount). Claims 10-15 have been cancelled without prejudice or disclaimer to the filing of a divisional application.

III. Claim Rejections Under 35 U.S.C. § 103

Claims 1-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bright et al., Abstract, 96th ASM General Meeting, pp. 220 (1996) (Bright et al. (a)), Bright et al., Abstract, Cystic Fibrosis Conference, pp. 225 (1995) (Bright et al. (b)), and further in view of U.S. Patent Application Serial No. 09/927885 to Mahan et al. (Mahan et al.), MacGregor et al., Journal of Bacteriology, pp. 5627-5635 (1996) (MacGregor et al.), O'Toole et al, Journal of Bacteriology, pp. 425-431 (2000) (O'Toole et al.), and WO Patent No. 98/03533 to Arrow et al. (Arrow et al.). More specifically, the Action states the following:

> Since Bright et al. (a) and (b) have taught the involvement of the crc locus in the regulation of the expression of *Pseudomonas aeruginosa* virulence factors, one of ordinary skill in the art would have been motivated to include catabolite repression control (crc) proteins in an assay for virulence inhibitors. One of ordinary skill in the art would have chosen a method of detecting the presence or absence of inhibition of crc protein and had a reasonable expectation of success since the art has taught the identification of crc protein in various crc mutant strains and FAA sensitivity as an assay of crc function. One of ordinary skill in the art would have been motivated to include oligonucleotides as inhibitors of bacterial virulence since Arrow et al. have taught the use of oligonucleotides to inhibit the growth of bacteria.

Action, page 7 (citation omitted). Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, three basic criteria must be met. First, the prior art reference or combination of references must teach or suggest all the claim limitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker,* 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143. Applicants respectfully submit that these criteria have not been met.

Applicants note that despite the number of references cited in the Action, none of the **six** references teach or suggest a method of screening for compounds that inhibit the virulence of

Pseudomonas bacteria as recited in Claim 1. Moreover, the six references cannot be properly combined where there is a lack of requisite suggestion or motivation to combine the references. For example, as the Action states, "Bright et al. (a) and (b) and Mahan et al., have not taught detecting the presence or absence of inhibition of the catabolite repression control (Crc) protein in an inhibitor of virulence assay." Action, page 6. These references also fail to suggest detecting the presence or absence of inhibition of the Crc protein in an inhibitor of virulence assay. Turning to the other cited references, MacGregor et al. proposes cloning and sequencing of the *crc* gene. *See* abstract. O'Toole et al. proposes a role of Crc in the signal transduction pathway that regulates biofilm development by *Pseudomonas aeruginosa*. *See* abstract. As stated in the present application at page 2, lines 10-16, the method proposed by Arrow et al. "is a general one and involves the integration of (1) methods for selecting the correct oligonucleotide, (2) synthesis and purification of nuclease resistant oligonucleotides, and (3) methods for in vitro analysis of potential antimicrobial oligonucleotides," and "[t]here remains a need for new ways to screen for antibiotics effective against *Pseudomonas*, along with compounds and methods of treating *Pseudomonas* infections." However, none of these additional references contain any suggestion to modify their teachings, or even combine their teachings, to arrive at a method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria as recited in Claim 1.

Furthermore, one of ordinary skill in the art to which the present invention pertains would not have been motivated to combine these six references based upon the teachings of these references where these references fail to suggest modification of their teachings or combination with other references teachings to arrive at a method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria. Instead, one of ordinary skill in the art would be motivated to combine these references only in view of the disclosure of the present application providing a method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria as recited in Claim 1, i.e., only in hindsight would one of ordinary skill in the art consult the six cited references.

In contrast to the assertions of the Action, Applicants also submit that even if the **six** cited references were combined, no reasonable expectation of success of arriving at the present

invention would exist. The mere assertion that "the art has taught the identification of crc protein in various crc mutant strains and FAA sensitivity as an assay of crc function" does not provide the basis for maintaining a reasonable expectation of success of arriving at method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria as recited in Claim 1. Again, it is only in view of the disclosure of the present invention that one of ordinary skill in the art is provided an enabling disclosure by which to arrive at the present invention. More specifically, Example 1 of the present application discloses the virulence of *crc+* and *crc-* employing the *Pseudomonas aeruginosa* in a mouse burn model. In this study, a wild-type strain of *Pseudomonas aeruginosa* designated PAO0001, a *crc* point mutation strain of *Pseudomonas aeruginosa* designated PAO8007, and a *crc* knock-out strain of *Pseudomonas aeruginosa* designated PAO8020, were tested in a burned mouse model of bacterial virulence. 200 cells of the indicated strain were injected into the burned skin wound of the animals. At 48 hours, post burn/infection death was observed in four of the five mice infected with PAO0001. Large numbers of PAO0001 were recovered from skin, blood, liver, spleen and other organs at death. This is similar to the mortality found in other strains of *Pseudomonas aeruginosa.*

In contrast, only one of five animals infected with PAO8007 was dead 48 hours after burn and infection (again with 200 bacterial cells), and all four remaining animals were still alive 7 days after burn and infection. Similar results were seen with animals infected with PAO8020.

This study was repeated with PAO8007 and PAO8020, but ten times the usual amount of bacteria was injected into the burn wound (i.e., 2,000 bacterial cells per animal). Essentially the same results were seen. Applicants note that the six cited references do not provide teachings or data that support such findings. Thus, even if the **six** cited references were combined, there is no reasonable expectation of success of arriving at the present invention.

Accordingly, Applicants respectfully submit that Claim 1, and claims that depend therefrom, are not unpatentable under 35 U.S.C. § 103(a) in view of Bright et al. (a), Bright et al. (b), Mahan et al., MacGregor et al., O'Toole et al., and Arrow et al. and request that this rejection be withdrawn.

IV. Conclusion

In view of the foregoing remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. Any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on December 18, 2002.

Vickie Diane Prior
Date of Signature: December 18, 2002

Version With Markings To Show Changes Made

Please replace the paragraph on page 17, lines 3-13, with the following paragraph as amended:

--**Abstract of the Disclosure**

The present invention relates to a **[A]** method of screening for compounds that inhibit the virulence of *Pseudomonas* bacteria and comprises the steps of: providing a culture medium comprising *Pseudomonas* bacteria; **[;]** administering a test compound to said bacteria, **[;]** and then detecting the presence or absence of inhibition of the catabolite repression control (Crc) protein in the **[said]** bacteria. **[,]** The **[the]** inhibition of the Crc protein indicates that the **[indicating said]** compound has antivirulence activity against *Pseudomonas* bacteria. Antisense oligonucleotides that inhibit expression of the Crc protein in a *Pseudomonas* bacteria and is nuclease resistant are also disclosed. Antivirulence compounds and the use thereof in treating *Pseudomonas* infections are also disclosed.--